The attached preliminary draft paper, “Status of Cumulative Risk Assessment Methodology for Organophosphate Pesticides,” dated August 22, 2001, was provided to a workgroup of the Committee to Advise on Reassessment and Transition (CARAT). This workgroup is focusing on advising the Agency on the development of a public participation process for the OP cumulative risk assessment. The attached document is being provided now so that the workgroup can advise the Agency on how to make it as useful as possible to stakeholders. Ordinarily this type of document would be released at the same time as the preliminary and/or revised risk assessment, to facilitate understanding of the assessment. Because the methods being used for cumulative assessment are new, and the OP cumulative risk assessment represents their first application, the Agency is seeking early input on this preliminary draft document. Ultimately, EPA intends that the document be completed based on feedback received from the CARAT workgroup and on the completed preliminary risk assessment. It would then be released as an accompaniment to the preliminary OP cumulative risk assessment.

August 22, 2001

STATUS OF CUMULATIVE RISK ASSESSMENT METHODOLOGY FOR ORGANOPHOSPHATE PESTICIDES

U.S. EPA Office of Pesticide Programs

August 22, 2001

Preliminary Draft

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I. Introduction

A. General

This document summarizes the basic principles that underlie OPP's evolving approach to cumulative risk assessment. It also describes the current status of the work on the organophosphate (OP) cumulative risk assessment. The subjects presented here are discussed more fully in the documents, "A Common Mechanism of Action: The Organophosphate Pesticides," dated November 2, 1998; "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity," dated February 5, 1999; "Guidance for Performing Aggregate Exposure and Risk Assessments," dated November 10, 1999; "Proposed Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity," dated June 22, 2000; "Endpoint Selection and Determination of Relative Potency in Cumulative Hazard and Dose-Response Assessment: A Pilot Study of Organophosphorus Pesticide Chemicals," dated September 5, 2000; "Cumulative Risk: A Case Study of the Estimation of Risk From 24 Organophosphate Pesticides," dated November 9, 2000; and "Preliminary Cumulative Hazard and Dose Response Assessment for Organophosphorus Pesticides: Determination of Relative Potency and Points of Departure for Cholinesterase Inhibition," dated July 31, 2001.

The purpose of this guide is to assist the reader by identifying and explaining the key features of the planned OP cumulative risk assessment. The guidance will help stakeholders better understand the assessment and the potential issues involved in the assessment and, ultimately, provide input on the conduct and conclusions of the assessments. Because the assessment itself is currently a work in progress, some areas of this guide provide more detail than others. In addition, it should be expected that some elements will change prior to the preliminary assessment and as a result of and otherwise following the public comment period on the preliminary risk assessment. Nevertheless, we have produced this document now, to facilitate as open and transparent a dialogue as possible. The document will be completed as an accompaniment to the public participation process on the preliminary risk assessment.

The documents noted above are posted on the Internet at: www.epa.gov/scipoly/sap/ or www.epa.gov/oppfead1/trac/science. The preliminary cumulative risk assessment for the OPs will be placed in the public docket in December, 2001. A 60-day public comment period on the preliminary risk assessment will follow the opening of the docket.

B. Common Mechanism Group/Cumulative Assessment Group

OPP has determined that it is appropriate to treat the organophosphates (OPs) as sharing a common mechanism of toxicity: the inhibition of cholinesterase activity. A cumulative assessment will be conducted to evaluate the combined risk from food, water, and residential/non-occupational exposure resulting from all relevant uses of OPs. Currently, the Agency is revising the proposed methodology it will use to conduct this assessment with guidance/advice provided by the FIFRA Scientific Advisory Panel and is completing work on the preliminary cumulative risk assessment of the OPs.

All of the OPs, which have been determined to cause a common toxic effect by the same or essentially the same sequence of major biochemical events, form the “Common Mechanism Group” or CMG for the OPs. The 40 chemicals in the CMG include the 39 OPs which are currently registered or have tolerances for import purposes as well as a new chemical fosthiazate. The new chemical, fosthiazate, will be examined in the assessment to determine if it might be considered for registration in the future. Fosthiazate is a potential methyl bromide alternative. The 40 members of the CMG are listed below in the Section “Common Mechanism Group/Technical Registrants.”

However, not all of these chemicals contribute meaningfully to the OP cumulative risk, for a variety of reasons, and therefore, some chemicals are not included in the assessment. The chemicals that are included in the cumulative risk assessment are referred to as the “Cumulative Assessment Group” or CAG. The 32 chemicals which form the Cumulative Assessment Group for the OPs is discussed below in the Section “Cumulative Assessment Group.”

C. Relationship Between Individual Chemical and Cumulative Assessments

To fully understand the goals and methods of the cumulative OP assessment it is necessary to understand the relationship of the individual OP risk assessments to the cumulative OP risk assessment. The individual assessments focus on a specific chemical, with the goal of deriving a "safe" level for its critical (most sensitive) effect. The individual assessment considers all endpoints and all exposures. The emphasis in the cumulative assessment is on the common mechanism effect shared by the group of chemicals, the relative potency of each chemical in producing the effect, and the likelihood of co-occurrence of exposures to the pesticides in the group. In general, the individual assessments should be done first. The aggregate assessments for the individual chemicals provide information needed to define the parameters of the cumulative exposure assessment. They permit evaluation of the strengths and weaknesses of the available data. This information is important for directing the process for deciding whether a particular pesticide source and/or pathway combination should be included in the cumulative assessment. In any case, it is necessary that both the individual and cumulative assessments be done, since they consider the risks of the chemicals in different ways.

As noted above, the cumulative risk assessment considers only the common mechanism endpoint. The effect identified as "common" may or may not be the effect that was used as the basis for establishing an individual chemical's endpoint. The common toxic effect may be produced at, above, or below doses that produce other toxicological effects that are not associated with the common mechanism of toxicity. For example, an OP may have an affect that is not associated with cholinesterase inhibition which may occur at a different dose level than the cholinesterase inhibition. In addition, because the emphasis is on the common effect, the endpoint selected for the cumulative assessment may be generally the same as in the individual assessment, for example the inhibition of cholinesterase, while the specific measure(s) used, for example plasma, red blood cell or brain, may be different for the two assessments.

The cumulative assessment considers only exposures relevant to a cumulative exposure assessment. The chemicals in the CAG must be determined to have an exposure potential that could result in the expression of a cumulative risk. Determining whether there could be concurrent exposure is a large consideration for CMGs that have short-term toxic effects as the common mechanism, as in the case of the OPs.

The risk of concern for the OPs is short-term. Therefore, the necessity to evaluate and consider <u>concurrent</u> exposures is extremely important because of the potential for fairly rapid onset of and recovery from the toxic effect. This is in contrast to, for example, most chronic and cancer endpoints for which the effect occurs after long-term exposure. In that case, concurrent exposures are not necessary for the chemicals to act by a common mechanism.

To analyze the potential for concurrent exposures, the exposure assessments for the OP cumulative risk assessment must address:

- ❏ Regional patterns in usage, which result in exposures to multiple chemicals that can be expected to occur only in a defined spatial or geographic area; and

- ❏ Temporal issues, for example, whether the pesticides are applied during the same season or time period, so that multiple exposures are possible, and the temporal relationship between exposures in food, water, and the home.

Exposure duration, pattern, and frequency, therefore, become paramount in determining where there is an opportunity for an individual to be exposed to two or more chemicals at the same time. In addition, to maintain the appropriate relationship between all of the components of the assessment (food, water, and residential), it is necessary to maintain the appropriate demographic element of the assessment, so for example, a two-year old's dietary exposure would not be combined with a homeowner applicator's exposure from treating his lawn. Finally, because the assessment combines many data sets into a single assessment, reducing the likelihood of compounding conservative assumptions and over-estimation bias becomes very important in constructing the cumulative risk assessment.

Developing a modeling tool that permits the assessment of co-occurrence is a necessary aspect of the development of cumulative methods. The model must be able to integrate exposure through food, water, and residential/non-occupational pathways to reflect both the probability of exposure by any given pathway and the timing of exposures through different pathways. Therefore, the model should reflect the exposure of discrete individuals/population members in which routes of exposure are linked and the estimated exposures reflect the individual's location, and other demographic characteristics of the individual such as age and weight; the time of year; the individual's anticipated patterns of pesticide use (for residential exposure); and the individual's history of exposure. For example, if an individual's house was treated for termites today, that exposure could continue for a period of time for that individual, but would not be randomly spread through a population. Similarly, for drinking water, the source of an individual's drinking water today is likely to be the same source tomorrow, and that spatial and temporal linkage must be preserved. The following chart illustrates how potential exposure to an individual/population member should consider and link temporal, spatial, and demographic components for the specific individual/population member.

Illustration of Exposure Linkages for an Individual in the Population

Example(s) of Individual Characteristics	*Dimension*	*Correlation for an Individual in the Population*
‣Person's Age ‣Season of the Year	*Temporal*	‣Age correlates with consumption pattern, activity pattern, inhalation rate ‣Drinking water consumption and residential pesticide application pattern consistent with season of year
‣Location of home (Urban or rural area, region of country)	*Spatial*	‣Drinking water estimates consistent with region of country ‣Residential pesticide usage likely for region of country
‣Gender	*Demographic*	‣Reproductive status consistent with age and gender ‣Personal preferences, behaviors, and characteristics consistent with data on home pesticide usage and type of home
Individual Example: An individual who is part of a population of concern is a 1-year old female, in New England, during the winter, in a rural location without municipal water, whose food consumption is that reported for her in the CSFII. She encounters potential residential pesticide use consistent with a rural, New England location in the winter. She does not apply home pesticides, but may come in contact with pesticides by crawling on the floor. Body weight, height, surface area, inhalation and other biological determinants are consistent with her other demographic characteristics, as recorded in the CSFII.		

The following chart summarizes the likely differences in the major exposure components of the risk assessments for the individual and cumulative assessments for food, water, and residential exposures and the resulting differences in the outputs of the assessments.

Differences in Individual OP Chemical And Cumulative OP Exposure Assessments

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Food	**Type of Assessment:**	Probabilistic	Probabilistic
	Input:	If an individual eats a particular food item, his probability of exposure to an individual chemical's residue is determined only by the probability of the residue being present on the food. In the individual assessments, estimates are made for all food items, and all the estimates are independently made, because it can be assumed that the probability of a single chemical being on any given item (say carrots) is unrelated to the probability of it being on any other item (say green beans) or to the probability of other chemicals being present on these items.	An individual's probability of exposure to multiple chemical residues depends not on the additive probabilities of the single chemical being present on a given food item, but on the probability of their co-occurrence on a single food item and across the multiple food items that the individual consumes. These probabilities, unlike with a single chemical, cannot be assumed to be independent of each other. Thus, for example, if a given field were treated with one OP for a particular pest, it would not be likely that it would also be treated with the other 15 OPs registered on that crop for that pest.
	Output:	Distribution of exposures for population of concern on a national scale.	Distribution of exposures for population of concern; however, these distributions will also be presented as regional distributions when integrated with the regional assessments being done for water and residential exposures.

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Water	**Type of Assessment:**	Deterministic	Probabilistic
	Input:	Uses a screening level conservative assessment, which uses a point estimate from a reasonable high-end exposure scenario, which is generally selected to represent all use areas for a given crop. The point estimate typically does not take into account seasonal variations in exposure concentrations. Thus, variations in exposure over time are not considered in the screening estimates. Such variation may be considered in more refined assessments, if sufficient information is available to do so, (e.g., water monitoring with frequent sample intervals). Point estimates are also used for water consumption values.	Uses a distribution of daily pesticide concentrations over 35 years rather than a single point estimate, and uses a regional approach based on geographic location, crops grown and agricultural practices as opposed to having one scenario represent all crops. Since determining the probability of co-occurrence or exposure to multiple pesticides at the same time is important to calculating total exposure for cumulative risk assessment, the timing of pesticide use, the place where the pesticide is used and the probability that it will occur in the drinking water in one or more regions is all being accounted for in order to develop reasonable exposures of pesticides in drinking water.
	Output:	Point estimate is compared to the residue level that could be in water and still be "safe," given the amount of residues estimated to be in food. This residue level is termed the Drinking Water Level of Comparison (DWLOC).	Distribution of exposures for populations of concern. These distributions will be presented as regional/site-specific estimates designed to represent the region of concern. They will be combined with exposure estimates from food, using food and water consumption data from CSFII as the common, linking factor.
	Analysis of Modeling Results:	When model estimates exceed the DWLOC, use all available refinements. Obtain all available monitoring data and compare to modeled values.	Model estimates will be refined as extensively as possible and will be compared to available monitoring data.

Exposure Pathways Element to Compare		*Individual Assessments*	*Cumulative Assessment*
Residential	**Type of Assessment:**	Deterministic	Probabilistic
	Input:	Individual exposure scenarios are developed to represent reasonable high-end exposures from application (homeowner applicators) and post-application exposures. The scenarios are generally taken to represent all areas of the country. Timing of exposure is not generally considered (except for the duration of exposure, for example, short-term, intermediate-term, or long-term).	Individual exposures are estimated along with the probability of co-occurrence with other exposures, all of which are presented, not in the context of the individual, but as probability distributions for the population of interest. To estimate co-occurrence the temporal and spatial aspects of residential use, together with the probability of use at any given time period are incorporated in the assessments. For example, termite applications would only be considered in certain areas of the country and lawn exposures would only occur at certain times of the year for most areas of the country. To establish these relationships, assessments are done for separate regions and for specific time periods.
	Output:	Risk estimates for individuals for representative scenarios, e.g., toddlers on a treated lawn, or combined applicator and post-application exposures for adults who treat their own lawn. These risk estimates are evaluated to determine if the use is "safe" for the individual/population member exposed.	Distribution of exposures for populations of concern, rather than for a specific individual/population member subject to the exposure. These distributions will be presented as regional/site specific estimates designed to represent the region of concern and will be combined with food and region-specific water exposure estimates.

In summary, it is important to see these two different assessments (individual chemical and cumulative) as distinct, in the questions they address, the methods they use, and the regulatory outcome that may be appropriate.

II. Common Mechanism Group/Technical Registrants

The following table lists the 40 OPs that are currently in the common mechanism group. This list includes the 39 OPs that are currently registered or have tolerances for import purposes, and also includes a new chemical, fosthiazate, which will be examined in the assessment to determine if it might be considered for registration in the future. Fosthiazate is a potential methyl bromide alternative. The table also shows the registrant(s) primarily responsible for the data on the chemicals (the "data-doers").

Chemical	*Registrant(s)*
Acephate	Valent
Azinphos methyl	Bayer
Bensulide	Gowan
Cadusafos	FMC
Chlorpyrifos	Dow
Chlorpyrifos methyl	Dow
Chlorethoxyfos	AMVAC
Coumaphos	Bayer
Diazinon	Syngenta; Mahkteshim-Agan
Dichlorvos	AMVAC
Dicrotophos	AMVAC
Dimethoate	Cheminova
Disulfoton	Bayer
Ethion	Cheminova
Ethoprop	Aventis
Ethyl Parathion	Cheminova
Fenamiphos	Bayer
Fenitrothion	Sumitomo
Fenthion	Bayer
Fosthiazate	ISK Biosciences
Malathion	Cheminova; Bayer
Methidathion	Gowan

Chemical	*Registrant(s)*
Methamidophos	Bayer
Methyl Parathion	Cheminova; Griffin; CerexAgri
Mevinphos	AMVAC
Naled	AMVAC
Oxydemeton Methyl (ODM)	Gowan
Phorate	BASF; Aceto
Phosalone	Aventis
Phosmet	Gowan
Phostebupirim	Bayer
Pirimiphos methyl	Agreliance
Profenofos	Syngenta
Propetamphos	Wellmark
Sulfotepp	Plant Products; Fuller
Temephos	Clark Mosquito Control
Terbufos	BASF
Tetrachlorvinphos	Boehringer Ingelheim Vetmedica; Hartz Mountain Corporation
Tribufos	Bayer
Trichlorfon	Bayer

III. Cumulative Assessment Group

As noted above, not all of the chemicals in the CMG contribute meaningfully to the OP cumulative risk, for a variety of reasons, and therefore, some chemicals may not be included in the assessment. In addition, while some chemicals and some chemical/use combinations are considered to be in the assessment, they will not necessarily be evaluated quantitatively. The following summarizes which OP chemicals the Agency currently plans to exclude from the CAG, and discusses several for which only qualitative assessments are likely to be performed. These decisions may change as the risk management for additional individual OP chemicals is completed.

A. Excluded Chemicals

Ethion, ethyl parathion, sulfotepp, cadusafos, fenitrothion, temephos, propetamphos, and coumaphos are currently not included in the cumulative assessment group, for the reasons discussed below.

Ethion, ethyl parathion, and sulfotepp are not included in the cumulative assessment group because these chemicals are being phased out according to specific legal agreements with the registrants. These legal actions call for a near term removal of the uses. In addition, the result of these actions in practice is often an accelerated move away from the chemical. As a result, if the Agency chose to include the chemicals in an assessment, it would be difficult to estimate the continuing exposure contribution. Finally, the Agency believes, given that these actions have already taken place, there could be an inappropriate regulatory effect if other chemicals or uses were considered for removal from the market now, as the result of considering these phased out uses in the assessment. It should be noted that phased out *uses* of certain other chemicals will also be excluded from the assessment.

Cadusafos, fenitrothion, temephos, and propetamphos are not included in the cumulative assessment group because it was determined in each of their individual assessments that there were negligible if any exposures. Cadusafos is used exclusively on imported bananas. No detectable food residues are expected from this use. Fenitrothion has a tolerance for imported wheat gluten from Australia and is used in the U.S. only in containerized bait stations in child resistant packaging. Monitoring data show negligible residues for wheat gluten, and exposure resulting from the containerized bait stations in child resistant packaging is expected to be insignificant also. Temephos is used only as a mosquito larvicide. Applications are limited to brackish water areas where exposure to both bystanders and drinking water is expected to be negligible.

Propetamphos is used only as a crack and crevice treatment. It is not allowed to be used in structures children or the elderly occupy, such as or including homes, schools, day-cares, hospitals, and nursing homes with the exception of areas of food service within those structures, when food is covered or removed prior to treatment. As the result of these restrictions, exposure is expected to be negligible.

Coumaphos is used for direct application to livestock and to swine bedding. The Agency anticipates that there is not likely to be appreciable transfer to meat and milk as the result of these uses.

B. Chemicals to Be Examined Qualitatively

Three chemicals–chlorethoxyfos, phostebupirim, and profenofos–have no detectable residues in PDP monitoring data and are each used on a single crop. They will likely not be included quantitatively in the assessment. However, a screening analysis for water will be conducted to assess whether their contribution to water exposure is also negligible.

C. Current Status of Each Chemical

The following table summarizes the current status of the OPs.

Organophosphates: Current Status

Chemical/Uses	*Included*	*Included: Qualitative Assessment Only*	*Excluded*	*Residential Use*
Acephate	✓			✓
Azinphos methyl	✓			
Bensulide	✓			✓
Cadusafos			✓	
Chlorethoxyfos		✓		
Chlorpyrifos	✓			✓ (qualitative only)
Chlorpyrifos methyl	✓			
Coumaphos			✓	

Chemical/Uses	*Included*	*Included: Qualitative Assessment Only*	*Excluded*	*Residential Use*
Diazinon	✓			
Dichlorvos	✓			✓
Dicrotophos	✓			
Dimethoate	✓			
Disulfoton	✓			✓
Ethion			✓	
Ethoprop	✓			
Ethyl parathion			✓	
Fenamiphos	✓			✓
Fenitrothion			✓	
Fenthion	✓			✓
Fosthiazate*	✓			
Malathion	✓			✓
Methidathion	✓			
Methamidophos	✓			
Methyl parathion	✓			
Mevinphos	✓			
Naled	✓			✓
Oxydemeton methyl (ODM)	✓			
Phorate	✓			
Phosalone	✓			
Phosmet	✓			
Phostebupirin		✓		
Pirimiphos methyl	✓			
Profenophos		✓		
Propetamphos			✓	

Chemical/Uses	*Included*	*Included: Qualitative Assessment Only*	*Excluded*	*Residential Use*
Sulfotepp			✓	
Temephos			✓	
Tetrachlorvinphos	✓			✓
Terbufos	✓			
Tribufos	✓			
Trichlorfon	✓			✓

*A new chemical being examined to determine if it might be considered for registration in the future–it is a potential methyl bromide alternative.

IV. Endpoint Selection

A. FQPA Safety Factor Determination

The Agency anticipates issuing in late September, at the same time that the revised guidance document on cumulative risk assessment is released, a science policy paper containing proposed guidance on the relationship of the FQPA Safety Factor to cumulative risk assessment. This document will further the policy development process to address questions surrounding how the FQPA Safety Factor relates to cumulative risk assessments. There will be an opportunity for public comment on this paper. Following the public comment on the document, EPA will consider the specific case of the OP cumulative assessment. Therefore, the preliminary OP cumulative risk assessment will likely not consider the FQPA safety factor.

B. Uncertainty Factors

1. Individual Chemical Uncertainty Factors

Chemical-specific uncertainty factors are applied, as appropriate, to the individual chemicals in the CAG, before considering the toxicity of the group. To begin this process, it is assumed that there are no uncertainty factors applied to the chemical, i.e., there are no uncertainty factors carried over from the individual assessments. Chemical-specific adjustments are based on issues with the toxicity data for an individual chemical, for example, to account for use of a LOAEL rather than a NOAEL or use of sub-chronic data in the absence of chronic data. These adjustments allow each chemical's database to express a uniform effect level, that is, allow them to provide equivalent measures of toxicity, to the extent possible.

2. Group Uncertainty Factor

The group uncertainty factor for the CAG is applied after estimating the toxicity of the group. The group uncertainty factor covers areas of scientific uncertainty that pertain to the group as a whole rather than to an individual chemical's database. This includes, for example, differences between species (inter-species) and among individuals within a species (intra-species). In addition, EPA analyzes any overall database uncertainty. This includes any issues concerning the quality and completeness of the database on the common toxic effect for the group as a whole.

C. Endpoint Selection & Relative Potency of Chemicals

Before an exposure assessment can be done, the chemicals must be ranked according to their ability to produce the toxic effect of concern. The common mechanism of toxicity for the OPs has been determined to be the inhibition of cholinesterase activity. The ability to produce this effect is quantified by a "potency" value. This method to estimate the relative potency of the OPs in producing the toxic effect of concern has been termed the "relative potency factor" method.

Using this method, the potency of each chemical is first calculated. Next an index chemical is selected. Finally, each chemical's potency is expressed in terms of the index chemical. The result of the method is the determination of a relative potency factor or RPF for each chemical. The table below shows the RPFs that have been developed. Only those chemicals which have residential/non-occupational exposures have RPFs for the dermal and inhalation routes of exposure. RPFs for ethoprop, fenthion, chlorpyrifos-methyl, and dicrotophos have not yet been calculated. These additional RPFs should be available by early September.

Relative Potency Factors

Chemical	*Oral*	*Dermal*	*Inhalation*
Acephate	0.02	0.002	0.18
Azinphos methyl	0.29		
Bensulide	0.02	0.001	NA
Chlorpyrifos	0.08		
Diazinon	0.12		
Dichlorvos	0.12	NA	20
Dimethoate	0.35		
Disulfoton	2.89	0.936	6.25
Fenamiphos	0.46	0.300	0.286
Fosthiazate	0.22		
Malathion	0.002	0.015	0.01
Methidathion	0.20		
Methamidophos (Index Chemical)	1.00	1.00	1.00
Methyl Parathion	0.25		
Mevinphos	0.37		
Naled	0.03	0.075	0.78
Oxydemeton Methyl (ODM)	0.81		
Phorate	2.46		
Phosalone	0.07		
Phosmet	0.10		
Pirimiphos methyl	0.03		
Terbufos	3.08		
Tetrachlorvinphos	0.002	0.001	NA
Tribuphos	0.23		
Trichlorfon	0.004	0.007	0.028

1. Calculating Relative Potency Factors

The relative potency factor for each chemical is expressed in relationship to an index chemical. The relative potency of the index chemical is, by definition, one. In the case of the oral route of exposure, each chemical's measure of potency is divided by the index chemical's measure of potency to produce its relative potency, as illustrated below.

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = 1$$

$$\text{Chemical A RPF} = \frac{\text{Chemical A Measure of Potency}}{\text{Index Chemical Measure of Potency}} = 0.5$$

$$\text{Chemical B RPF} = \frac{\text{Chemical B Measure of Potency}}{\text{Index Chemical Measure of Potency}} = 2.0$$

In this example chemical A is half as potent as the index chemical in producing the effect of concern, while chemical B is twice as potent as the index chemical in producing the effect.

In the case of the dermal and inhalation routes of exposure, the division is reversed, that is the index chemical's measure of potency is divided by each chemical's measure of potency to produce that chemical's relative potency. It was necessary to reverse the division, because two different methods were used to derive the measures of potency–one for the oral route of exposure and another for the dermal and inhalation routes. These two methods yield results that are inverse of each other. The oral Relative Potency Factors are calculated using enzyme *activity* while dermal and inhalation Relative Potency Factors are calculated based upon percent *inhibition*. As a result of reversing the division, as the relative potency increases the Relative Potency Factors increase for all routes of exposure. Therefore, a higher Relative Potency Factor always means a higher relative potency. The reversed division has absolutely no effect on what the *relative* potencies are. The calculation for the dermal and inhalation routes is illustrated below.

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = 1$$

$$\text{Chemical A RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Chemical A Measure of Potency}} = 0.5$$

$$\text{Chemical B RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Chemical B Measure of Potency}} = 2.0$$

In this example also, chemical A is half as potent as the index chemical in producing the effect of concern, while chemical B is twice as potent as the index chemical in producing the effect.

<u>Use of Relative Potency Factors to Express All Residues As Residues of the Index Chemical</u>

After calculating the relative potencies of all of the chemicals in the CAG, for each exposure route and duration that is being assessed (e.g., oral/acute), the residues of each chemical are multiplied by that chemical's relative potency factor for each exposure of interest (e.g., food residues). Where these residues can co-occur to the same population member, the resulting values are added together to get the total, cumulative exposure in terms of residues of the index chemical, as illustrated below.

$$\begin{array}{r} \text{Residue Index Chemical} \times 1.0 \\ \text{Residue Chemical A} \times 0.5 \\ +\text{Residue Chemical B} \times 2.0 \\ \hline \text{Total Residues (expressed as} \\ \text{residues of the index chemical)} \end{array}$$

Implementing the Relative Potency Factor Method

The method itself, as illustrated above, is straightforward; however the details of its implementation in any given case are more complex. In order to implement the method, four critical pieces are necessary.

- ❑ Selection of a specific common endpoint (e.g., plasma, brain, or RBC cholinesterase inhibition in male or female rats, rabbits, dogs, or mice) and duration of exposure on which to compare potencies;

- ❑ Estimation of the dose-response curves and calculation of the relative potencies;

- ❑ Selection of an index chemical; and

- ❑ Selection of the specific level of response (e.g., BMD_{10} or NOAEL) to represent the toxicity of the index chemical. This is referred to as the Point of Departure (PoD). [A Bench Mark Dose (BMD) is an estimated dose level associated with some designated level or percent of response relative to the control or baseline level of response. For example, the BMD_{10} is a dose associated with a 10% response.]

The index chemical is selected based on which chemical in the CAG has the best data base for all routes of exposure (oral, dermal, inhalation) and has the best-characterized dose-response curve for the toxic effect. This allows a more reliable analysis of all the potential data available on the relative potencies of the other chemicals. The selection of the index chemical does not affect the individual chemical potency values used to calculate the relative potencies. The importance of the index chemical selection lies in the determination of the dose level used in risk estimation (the Point of Departure mentioned above). This dose level can be a benchmark dose or a NOAEL. It is desirable to have high confidence in the selected dose levels. Therefore, again, it is desirable that the index chemical have the best and most complete toxicity data base for the common endpoint.

Selection of a specific common endpoint, duration of exposure, and the method to compare potencies is based on a detailed analysis of the toxicity database. In presentations to the Scientific Advisory Panel (SAP), the Agency has discussed several approaches that could be used. The Agency has implemented the suggestions of the SAP in its latest document on the hazard and dose-response assessment for the OPs ("Preliminary Cumulative Hazard and Dose Response Assessment for Organophosphorus Pesticides: Determination of Relative Potency and Points of Departure for Cholinesterase Inhibition," dated July 31, 2001). The approach described in this paper reflects the previous feedback provided by the SAP. Another Scientific Advisory Panel meeting to review this work is planned for September 5 and 6, 2001.

The Agency used two different methods to select the measures of potency, one for the oral, and another for the dermal and inhalation routes of exposure. This was necessary because there are different amounts of data available for the different routes. Determination of the relative potency for the dermal and inhalation routes of exposure will be discussed first, because these are the simplest cases. This will be followed by discussion of the oral route and the selection of the index chemical, which is the same chemical for all routes of exposure.

<u>Determination of the Relative Potency Factors for the Dermal and Inhalation Routes of Exposure</u>

The dermal and inhalation routes of exposure are only applicable to residential exposures. Therefore, RPFs were only determined for the chemicals that have residential uses and are likely to be included quantitatively in the assessment. Fenthion was added to this group after the original set of RPFs had been determined. Fenthion's RPF is in the process of being determined. Adding chemicals to the CAG and calculating relative potencies for them has no effect on the relative potencies of the other chemicals. Each chemical's measure of potency is calculated independently and then compared to that of the index chemical.

2. Dermal Relative Potency Factors

Relative potencies for the dermal route of exposure were determined using NOAELs observed in dermal toxicity studies. This is in contrast to the relative potency factors for the oral route which, as will be discussed shortly, were determined through modeling. The dermal studies were chosen because of the importance of using the same route of exposure, in this case dermal, for both the toxicity evaluation and the exposure estimate. There are, however, only a limited number of dermal studies with high quality dose-response data. Therefore, it was determined that the database of dermal toxicology studies, when considered across all of the chemicals, was not appropriate for dose-response modeling. Since it is preferred to use the same measure of potency for all of the chemicals, when determining *relative* potency, this necessitated using the NOAELs as the measure of potency.

As noted above, determination of relative potencies based on tests using the same sex and species is preferred. As will be explained in detail when oral relative potencies are discussed, the Agency has concluded based on an evaluation of all the available data, that the data on inhibition of cholinesterase activity in male rat red blood cells (RBC) is the best measure of relative potency for cumulative risk assessment. Therefore, NOAELs for male RBC cholinesterase inhibition from dermal toxicity studies were used to determine the dermal relative potency measures. The NOAEL was defined as the lowest dose where no more than 10 to 15% RBC cholinesterase inhibition (compared to the control) occurred.

In the case of dermal exposure, tests on the same species were not always available. Four chemicals were tested by the dermal route in rats. Only rabbit studies were available for four OPs. Thus, both rat and rabbit data were used.

One chemical, dichlorvos, had no dermal exposure study of any kind. OPP waived the requirement for a dermal toxicity study due to the volatility of the chemical, which makes it very difficult to conduct such a study. It has not yet been determined whether or how residential/non-occupational dermal exposure will be assessed for dichlorvos in the preliminary cumulative risk assessment of the OPs.

Based on the above considerations, the following NOAELs were chosen as the measures of potency for the dermal route of exposure.

Measures of Potency for the Dermal Route of Exposure: NOAELs for Male RBC Cholinesterase Activity from Dermal Toxicity Studies

Chemical	*Species*	*Male NOAEL(mg/kg/day)*
Acephate	rat	300*
Bensulide	rat	500*
Dichlorvos	Dermal exposure study waived due to volatility of compound.	
Disulfoton	rabbit	0.8
Fenamiphos	rabbit	2.5
Malathion	rabbit	50
Methamidophos	rat	0.75
Naled	rat	10
Tetrachlorvinphos	rat	1000*
Trichlorfon	rabbit	100

* Highest dose tested.

The following examples illustrate how these NOAELs are used to calculate the relative potency factors. Using the measure of potency for the index chemical, 0.75 mg/kg/day, as explained above, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.75}{0.75} = 1$$

$$\text{Acephate RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Acephate Measure of Potency}} = \frac{0.75}{300} = 0.002$$

$$\text{Bensulide RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Bensulide Measure of Potency}} = \frac{0.75}{500} = 0.001$$

The remaining relative potencies can be calculated in a similar manner. All of the available RPFs for the dermal route of exposure are listed in the table at the beginning of this section.

3. Inhalation Relative Potency Factors

Relative potencies for the inhalation route of exposure were determined using NOAELs from inhalation toxicity studies. This is in contrast to the relative potency factors for the oral route which, as will be discussed shortly, were determined through modeling. As described in the case of dermal exposure, the inhalation studies were chosen because of the importance of using the same route of exposure, in this case inhalation, for both the toxicity evaluation and the exposure estimate. As in the case of the dermal toxicity database, the number of available inhalation toxicity studies with quality dose-response data was limited. Therefore, it was determined that the database of inhalation toxicology studies, when considered across all of the chemicals, was not appropriate for dose-response modeling. Since it is preferred to use the same measure of potency for all the chemicals, when determining *relative* potency, this necessitated using the NOAELs as the measure of potency.

As noted above, determination of relative potencies based on tests using the same sex and species is preferred. As will be explained in detail in the section below on “Oral Relative Potency Factors,” the Agency has concluded based on an evaluation of all the available data that, for the OPs, the data on inhibition of cholinesterase activity in male rat red blood cells (RBC) is the best measure of relative potency for cumulative risk assessment. Therefore, NOAELs for male RBC cholinesterase inhibition from inhalation toxicity studies were used to determine the inhalation relative potency measures. The NOAEL was defined as the lowest dose where no more than10 to15% RBC cholinesterase inhibition (compared to the control) occurred.

All of the inhalation studies were performed with the same species (rat); however four different strains of rats were used. The exposure conditions varied among the chemicals tested. Four used whole-body exposure while three used nose only exposures. The studies were sub-chronic (21 to 90 days), with the exception of dichlorvos, which had only a chronic inhalation study.

No inhalation toxicity studies were available for two chemicals, bensulide and tetrachlorvinphos. It has not yet been determined whether or how residential/non-occupational inhalation exposure will be assessed for these two chemicals in the preliminary cumulative risk assessment of the OPs.

Based on the above considerations, the following NOAELs were chosen as the measures of potency for the inhalation route of exposure.

Measures of Potency for the Inhalation Route of Exposure: NOAELs for Male RBC Cholinesterase Activity from Inhalation Toxicity Studies

Chemical	*Method (species tested was the rat in all cases)*	*Male NOAEL (mg/L)*
Acephate	nose only	0.0056*
Bensulide	No inhalation toxicity study available.	
Dichlorvos	whole body	0.00005
Disulfoton	nose only	0.00016
Fenamiphos	nose only	0.0035*
Malathion	whole body	0.1
Methamidophos	head/nose	0.001
Naled	whole body	0.0013
Tetrachlorvinphos	No inhalation toxicity study available.	
Trichlorfon	whole body	0.035

* Highest dose tested.

These NOAELs are used to calculate the relative potency factors in exactly the same way as in the case of the dermal RPFs. Using the measure of relative potency for the index chemical, 0.001 mg/L, as explained above, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.001}{0.001} = 1$$

$$\text{Acephate RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Acephate Measure of Potency}} = \frac{0.001}{0.0056} = 0.18$$

$$\text{Dichlorvos RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Dichlorvos Measure of Potency}} = \frac{0.001}{0.00005} = 20$$

The remaining relative potencies can be calculated in a similar manner. All of the available RPFs for the inhalation route of exposure, are listed above.

4. Oral Relative Potency Factors

Model Used to Estimate RPFs for the Oral Route of Exposure

In the case of the oral route of exposure, numerous oral studies with comparable methodologies are available and suitable for dose-response analysis. Therefore, it was possible to determine relative potency factors for the oral route of exposure using a model developed in response to SAP comments. In response to the pilot analysis presented in September 2000, the SAP provided the following recommendations, which were implemented in the current approach.

❑ There would be much greater confidence in the measure of relative potency if it were derived from several, relatively consistent studies as opposed to a single study, without benefit of confirmation by other studies.

❑ The panel suggested the Agency reevaluate the selection of the probit model for determining the relative potencies. They specifically suggested considering Michaelis-Menton kinetics or an exponential model as the potential alternative methods.

Following analysis of all the available oral data, it was determined that an exponential function best described the dose-response relationship observed across the studies. The following exponential equation was used to model the dose-response curves.

$$y = B + (A - B) \times e^{-m*dose}$$

where:

y=cholinesterase activity
B=the y-asymptote
A=background cholinesterase activity
m=slope scaling factor (the measure of potency)
Dose=dose of the OP, in mg/kg/day

While the equation itself may appear rather daunting, the idea is fairly simple. All of the relevant data points are assembled and the equation employs a mathematical exercise, called generalized least squares regression, that attempts to find a curve that comes the closest to the most data points (simultaneously) as possible. Statistics are then available to assess if this curve is really a good representation of these data points. If the curves that are developed using this equation are a good representation of the data, then the slope scaling factor, m, is a good representation of the relative potencies.

This model did provide a good representation of the data. Out of a total of 1312 data sets available for modeling, the above exponential function was a good representation of the dose-response for 1306 data sets. Further analysis of the potency estimates showed that the estimates in most of the remaining six data sets where it was not a good fit, were comparable to the potency estimates for the rest of the data. A data set in this case consisted of the cholinesterase measurements at a specific time point from a specific study for a specific compartment (plasma/RBC/brain) and sex combination (e.g., male/plasma).

The dose-response analysis was performed using a computer program developed for this purpose by the Agency's Office of Research and Development's National Health and Environmental Effects Laboratory (NHEERL). This program, OPCumulativeRisk (OPCumRisk), is publicly available on the internet at www.epa.gov/scipoly/sap/index.htm#september.

Selection of Species/Compartment/Sex and Duration of Exposure for Comparison of Potencies

Relative potency should be determined using a uniform basis of comparison. This requires using to the extent possible a common response derived from a comparable measurement methodology, species, and sex for all the exposure routes of interest. Although many different methods are available for measuring cholinesterase activity, for this assessment they are all assumed to be comparable if the study was found to be acceptable. Although studies are available for various species (e.g., dog, mouse, rat, and rabbit), toxicology studies in the rat provided, by far, the most extensive cholinesterase activity data for all routes (dermal, inhalation and oral) and in the three compartments (plasma, red blood cell, and brain) in both sexes. Therefore, for the oral route, only rat studies were used in determining relative potencies.

The Agency decided to use only those data that reflect steady-state conditions for cholinesterase inhibition to estimate relative potencies. Steady-state as used here describes the time point in a multi-dose study at which additional doses result in no further increase in cholinesterase inhibition. This was done because the steady state values produce relative potency factors that are reproducible and reflect less uncertainty due to the rapidly changing, time-sensitive differences in measures of cholinesterase that are observed prior to achieving a steady-state. Steady-state for each OP was determined qualitatively. This analysis showed that most chemicals appeared to reach steady-state by 21 to 28 days of exposure in both sexes and all three compartments (plasma, RBC, and brain). As a result, only cholinesterase measures based on study duration of 21 days or longer were used in the development of the RPFs. The available data sets for each chemical-sex-compartment included a range of exposure durations from 21 days to greater than 700 days.

The SAP also recommended against combining data (at least initially) across compartments, i.e., plasma, red blood cell (RBC), and brain, or for males and females. This led the Agency to analyze six separate compartment/sex combinations for each chemical, i.e., male/plasma; male/RBC; male/brain; female/plasma; female/RBC; and female/brain. These were analyzed in order to determine an appropriate compartment/sex on which to compare potencies of the chemicals. Overall there is a good agreement between potency values calculated for males and females, with the notable exception of tetrachlorvinphos for which the male/brain potency value is over 15X larger than the female value. Therefore, the selection of either males or females would make little difference in the RPFs. Males were chosen for use in the comparison of potencies.

For most of the chemicals, the relative potencies were similar when calculated using plasma, RBC, and brain measurements. There are two notable exceptions to this observation. Potencies of diazinon and fenamiphos are 20 to 100X larger in the RBC and plasma cholinesterase measurements than in the whole brain. In considering which compartment to use for the RPF measure, it was noted that the brain cholinesterase activity data has limitations compared to the blood data, mainly because brain cholinesterase activity was generally only measured at the end of the study. Thus, time course information is rarely available. In general, the number of available studies and the quality of dose-response data for plasma and RBC inhibition was essentially the same. Furthermore, when the potency factors for RBC and brain are compared for all of the OPs in the analysis, the RBC relative potency is a good predictor of the brain relative potency for the majority of the chemicals. Therefore, RBC cholinesterase inhibition was chosen for comparison of potencies.

In summary, the oral relative potency values are based on cholinesterase activity data derived from male rat RBC data, taken from studies that lasted 21 days or longer. This choice was made after an extensive analysis of all available oral data. As we have seen, such extensive databases are not available for the dermal and inhalation routes of exposure. Therefore, because of the extensive oral database, which makes a detailed comparison between compartments for males and females possible, this same selection of male rat RBC data was also used in the case of the dermal and inhalation routes. The only exception is when rat data were not available for the dermal route of exposure. In addition, as we will see shortly, the same selection was made for determining the points of departure for risk assessment.

After determining that male RBC measures in the rat were the most appropriate for comparison of relative potency factors, the RPFs can be calculated using the slope scaling factor, m, from the above exponential equation as the measure of potency. These slope scaling factors for each chemical are listed in the table below.

Slope Scaling Factors (m in the exponential equation)

Chemical	*Slope Scaling Factor (m)*
Acephate	0.021
Azinphos methyl	0.35
Bensulide	0.026
Chlorpyrifos	0.102
Diazinon	0.15
Dichlorvos	0.14
Dimethoate	0.431
Disulfoton	3.55
Fenamiphos	0.56
Fosthiazate	0.27
Malathion	0.0042
Methidathion	0.25
Methamidophos (Index Chemical)	1.23
Methyl Parathion	0.30
Mevinphos	0.46
Naled	0.03
Oxydemeton Methyl (ODM)	0.99
Phorate	3.02
Phosalone	0.09
Phosmet	0.12
Pirimiphos methyl	0.032
Terbufos	3.79
Tetrachlorvinphos	0.00246
Tribuphos	0.28
Trichlorfon	0.00479

The following illustrates how these slope scaling factors are used to calculate the relative potency factors. Using the measure of potency for the index chemical, 1.23 mg/kg/day, as explained above, the relative potency factors are calculated as:

$$\text{Index Chemical RPF} = \frac{\text{Index Chemical Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{1.23}{1.23} = 1$$

$$\text{Acephate RPF} = \frac{\text{Acephate Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.021}{1.23} = 0.02$$

$$\text{Bensulide RPF} = \frac{\text{Bensulide Measure of Potency}}{\text{Index Chemical Measure of Potency}} = \frac{0.026}{1.23} = 0.02$$

Where the Measures of Potency for all of the chemicals are the values of m in the exponential equation calculated using that chemical's male rat RBC data, from studies 21 days or longer.

The relative potencies for the remaining chemicals can be calculated in a similar manner. All of the available RPFs, for the oral route of exposure are listed in the table at the beginning of this section.

<u>Selection of the Index Chemical and the Points of Departure for Risk Assessment</u>

The index chemical is selected based on which chemical in the cumulative assessment group has the best data base for all routes of exposure (oral, dermal, inhalation) and the best-characterized dose-response curve for the toxic effect. It is important that it acts toxicologically as purely as possible by the common mechanism defining the group, that is, it has no other modes of appreciable toxicity; and that quantitative data for assessing potency be available for as many routes of exposure, genders, species, and strains of animals as possible. This allows a more reliable analysis of all the potential data available on the relative potencies of the other chemicals.

Methamidophos was chosen to be the index chemical for the OP cumulative assessment. The oral database contains studies that characterize the entire dose-response range from very low doses to high doses. Within the oral route of exposure, potency values for methamidophos were consistent between adult male and female rats and among the three compartments (plasma, RBC, and brain). Quality dose-response data were also available for the dermal and inhalation routes of exposure. Dermal toxicity studies in two species show comparable NOAELs and an inhalation study is available where multiple blood cholinesterase measurements were taken. Available data from the literature support the conclusion that methamidophos acts "toxicologically as purely as possible." It is a direct-acting anti-cholinesterase OP that appears to selectively inhibit cholinesterase, the target enzyme.

The selection of the index chemical does not affect the potency values used to calculate the relative potencies for the individual chemicals, since these are based solely on the individual chemical's data, nor does it affect the relative potencies of the chemicals, which is simply an indexing exercise. The importance of the index chemical selection lies in the determination of the dose level that will be used in risk estimation. This dose level is called the Point of Departure or PoD. It can be an observed NOAEL from a single study, as was the case in the individual OP risk assessments, or it can be based on a modeled estimate of the no effect level, which is referred to as a benchmark dose.

The oral, dermal, and inhalation PoDs for the cumulative assessment are based on benchmark dose modeling of the rat male RBC data for studies of 21 days or longer for methamidophos. The benchmark dose where cholinesterase activity is reduced by 10% compared to background activity (BMD_{10}) is the effect level selected. OPP has traditionally used 10% cholinesterase inhibition for plasma and RBC as the decision-point for selecting an effect level when cholinesterase inhibition is the effect of interest. These PoDs are listed in the following chart. They are the endpoints the Agency plans to use in the preliminary OP cumulative risk assessment.

Points of Departure (from the Index Chemical Methamidophos): Male Rat RBC Cholinesterase Activity from Toxicity Studies 21 Days or Longer

Route of Exposure	*BMD_{10}*
Oral	0.09 mg/kg/day
Dermal	1.21 mg/kg/day
Inhalation	0.0046 mg/L

Why a Benchmark Dose?

As a result of the extensive and high quality data base for methamidophos, it is possible to reliably model the dose-response for all three compartments. When the available data allow reliable modeling, it is possible to estimate the “true” no effect level from a curve that has been developed using all of the data, in a manner similar to what was described above, for the exponential function. This approach allows one to take into account the full dose-response curve and calculate measures of variability (confidence limits) on the estimated BMD. It is not dependent on the dose levels selected in the studies, although to obtain a reliable model curve, adequate dosing is a necessity. Therefore, to take advantage of all of the available information for methamidophos, dose-response curves were modeled for each route of exposure using all of the male rat RBC data available from studies 21 days or longer to give the most reliable PoDs possible. The analysis of the data also showed that male and female plasma and brain BMD_{10}'s were similar to the male RBC BMD_{10}'s, and confidence limits on the estimates were fairly tight. These observations increase the confidence in the selection of methamidophos as the index chemical.

Although it was possible to model the dermal and inhalation data for methamidophos to obtain benchmark doses for the dermal and inhalation Points of Departure, for the other chemicals only a limited number of dermal and inhalation studies with quality dose-response data were available. Thus, in calculating RPFs, it was necessary to rely on NOAELs rather than use benchmark doses or slope scaling factors.

5. Summary and Example

Three elements are required for endpoint selection in the case of cumulative assessments: selection of an index chemical, calculation of relative potency factors, and selection of points of departure. These elements perform exactly the same function as the elements in an individual chemical assessment, although more elements are used in a cumulative assessment, and some of them are referred to by different terms. Therefore, the following summary relates the elements used in the cumulative assessment back to the basic risk assessment equation that is used in all risk assessments:

Risk = Hazard x Exposure

The exposure part of the equation is obtained by summing all of the relevant residues to which a person is exposed, for the relevant time period. In individual chemical assessments these residues can simply be added together, because they are all residues of the same chemical. In a cumulative assessment these residues must first be put on a common scale before they can be added. This is done by multipling each residue by a number which represents it's potency as shown below.

Residues		Relative Potency Factor		Residues Expressed as Residues of the Index Chemical
1 mg Chemical A	X	0.5	=	0.5 mg
2 mg Chemical A	X	0.5	=	1.0 mg
0 mg Chemical B	X	2.0	=	0.0 mg
3 mg Chemical B	X	2.0	=	6.0 mg
2 mg Chemical	X	1.0	=	2.0 mg
4 mg Chemical	X	1.0	=	4.0 mg
				13.5 mg /day of the index chemical

Once all of the residues have been converted by this process, the "Exposure" side of the equation is exactly the way it is for an individual chemical–it is as if all of the residues are residues of the index chemical.

Just as in the case of an individual chemical assessment the "Hazard" part of the equation is obtained by selecting the dose levels that will be used for risk assessment. Since all of the residues are now expressed in terms of the index chemical, the dose levels for use in risk assessment are selected for the index chemical and compared to the residues, to obtain the estimate of risk.

For example, to perform a dermal risk assessment using an MOE approach, the methamidophos point of departure for dermal risk assessment, 1.21 mg/kg/day, and the above exposure estimate,13.5 mg/day of methamidophos (converted to mg/kg/day by dividing by body weight = 13.5÷ 62 kg = 0.22 mg/kg/day), would be used to calculate the following MOE.

$$\text{MOE} = \frac{\textbf{\textit{Hazard}}}{\textbf{\textit{Exposure}}} \quad \textbf{\textit{or}} \quad \textbf{\textit{MOE}} = \frac{\textbf{\textit{Point of Departure}}}{\text{Exposure}} = \frac{\textbf{\textit{1.21}}}{\textbf{\textit{0.22}}} = \textbf{\textit{5.5}}$$

The "new and complicated" part of the OP cumulative risk assessment is determining (and keeping track of) what measures should be used for relative potency, and what points of departure for the index chemical should be used in risk assessment. The measures of potency were selected to provide the best measures of *relative* potency. The points of departure were selected to provide the best measures of the index chemical's toxicity for use in risk assessment. All of the measures of potency for each route (dermal, inhalation, and oral) are listed in the tables above, as are the points of departure for methimidophos. The following provides a summary of what measures were used in each case.

Route of Exposure	*Measure of Potency*	*Point of Departure*
Dermal	NOAELs (from a single dermal study for each chemical using male rat RBC and a study 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on male rat RBC from one methamidophos dermal study)
Inhalation	NOAELs (from a single inhalation study for each chemical using male rat RBC and a study 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on male rat RBC from one methamidophos inhalation study)
Oral	Slope Scaling Factors (m) (modeled using all acceptable oral studies for each chemical using male rat RBC from studies 21 days or longer)	BMD_{10} (modeled from Methamidophos Dose-Response Curve based on male rat RBC from three methamidophos oral studies 21 days or longer)

V. Cumulative Exposure Models

Developing a modeling tool that permits the assessment of co-occurrence is a necessary aspect of the development of cumulative methods. The model must be able to integrate exposure through food, water, and residential/non-occupational pathways in a manner that reflects both the probability of exposure by any given pathway and the timing of exposures through different pathways. This means the model should reflect the exposure of discrete individuals/population members in which routes of exposure are linked and the estimated exposures should reflect the individual's location, and other demographic characteristics of the individual such as age and weight; the time of year; the individual's anticipated patterns of pesticide use (for residential exposure); and the individual's history of exposure. For example, if an individual's house was treated for termites today, that exposure could continue for a period of time for that individual, but would not be randomly spread through a population. Similarly, for drinking water, the source of an individual's/population member's drinking water today is likely to be the same source tomorrow and that spatial and temporal linkage must be preserved. As a result, the building blocks for the cumulative risk assessment are specifically defined individuals/population members for whom the spatial, temporal, and demographic aspects of their exposures are linked. The anticipated outputs that will likely be presented are:

- ❑ Cumulative risk from OPs in foods
- ❑ Cumulative risk from OPs in drinking water
- ❑ Cumulative risk from OPs in residential/non-occupational settings
- ❑ Cumulative risk from OPs across multiple pathways (food, water, and residential/ non-occupational)
- ❑ All of the above assessments may contain some elements that are dealt with qualitatively

This paper will describe the attributes of one software model, Calendex™, in some detail. In addition, the attributes and current status of other models that allow assessment of cumulative risks will be reviewed. Calendex™ is a proprietary software package licensed from Novigen Sciences, Inc. The Calendex™ model and its dietary component, DEEM™, have been the subject of review at two SAP meetings. [The following papers were presented at those meetings: "Dietary Exposure Evaluation Model (DEEM™) and DEEM™ and Max LIP (Maximum Likelihood Imputation Procedure) Pesticide Residue Decompositing Procedure and Software," dated February 29, 2000 and "Calendex™; Calendar-Based Dietary & Non-Dietary Aggregate and Cumulative Exposure Software System," dated September 27, 2000].

Calendex™ contains demographic and food consumption data for a sample of individuals/population members that is representative of the U.S. population. This is the CSFII (USDA's Continuing Survey of Food Intakes by Individuals) for 1994-1996 together with the 1998 Supplemental Children's Survey. The demographic variables (e.g., age, sex, weight) for each individual/population member in the survey can be used as part of the basis for selecting potential non-food exposures for the individuals as well as to link these non-food exposures to the food exposure for these individuals. For each scenario that is developed, routes can be linked if exposures are dependent on each other. If the exposures are linked, then the model assumes that the exposures occur at the same time, for example, the inhalation and dermal exposures that result from a pet flea dip application should occur on the same day. Calendex™ uses the calendar day as the unit of time for calculating exposure. If exposure estimates for more than one day are required, these are built by adding together sequential daily exposures and averaging them over the number of days to provide an average daily exposure over the desired time frame. If single-day exposures are considered, the output of the analysis is a distribution of daily exposures.

Calendex™ calculates daily food exposure using the DEEM™ dietary exposure model OPP currently uses for individual chemicals. In the cumulative analysis, however, the time component is preserved so that the food residues are estimated for every single day of the year, so that they can be combined with daily drinking water and residential exposures. Thus, the output of the food analysis is multiple years of daily exposures through food. Drinking water concentrations are related in time. The pesticide concentration in drinking water at a particular site on day 1 is correlated with the concentration on day 2. The model must preserve this time-series relationship. A similar relationship exists for residential exposures.

Calendex™ would use the following steps to estimate food and water exposures in the case of single day exposures. It would calculate exposure from food for individual #1 using one of his two diets in the CSFII. For water, it would select a random year from any data set for which multiple years of daily concentrations are available, and calculate the water exposure on January 1. This could be, for example, daily distributions estimated with PRZM/EXAMS (IR-PCA), which provides a robust distribution of daily concentrations over a wide range of years, or monitoring data, which generally do not provide daily water concentrations or more than a few years of monitoring. In the case of monitoring that does not include daily values, a concentration might be selected to be representative of each day. Calendex™ would calculate the exposure from water for individual #1 by multiplying the concentration in water by the water consumption reported in the CSFII by individual #1 and then sum the total exposure for food and water for individual #1 on that day. The calculations would be repeated for the next calendar day from the same year until a distribution of single-day exposures is generated for the entire year. The resulting distribution preserves the effect of annual weather events on the anticipated water residues. These steps would then be repeated for another randomly selected year. The above steps would then be repeated for all individuals/population members in the CSFII. Finally, the whole process would then be repeated for each region. The output would be a distribution of exposures for the population subgroups of concern for each region.

Calendex™ uses the following analogous steps to calculate residential/non-occupational exposures. It uses the probability that individual exposures occur and the specific dates for those exposures to calculate exposure for individual chemical uses and exposure routes. Then Calendex™, combines these exposure probability distributions for the individual using probabilistic techniques, that is, repeatedly sampling from the individual distributions to get a combined probability distribution for the individual's total exposure. In doing these calculations the model is able to use information on the frequency and amount of chemical used and the degradation of the chemicals over time. The estimates of the amount of residues available to be contacted, how easily they dislodge (i.e., come off) when contacted, and how often contact is made are provided as inputs into the model, and may be distributions or point estimates.

The Agency has worked extensively with the components of Calendex™ and has developed the capability to track inputs, corresponding to individual daily outputs, back to specific pesticide residue inputs, including the source pesticide and commodity or use of the pesticide in an agricultural or residential setting. As such, Calendex™ will permit the Agency to identify sources of exposure in order to identify further refinements or mitigation strategies.

The Agency is aware of three other models that have been developed or are under development to conduct multi-pathway assessments and that can be adapted to incorporate inputs for data from multiple chemicals. Two of these have been presented to the SAP as aggregate risk assessment models: LifeLine™, a model developed by Hampshire Research Institute, currently licensed by the LifeLine Group; and Rex™, a product of Infosciences. Neither of these packages appears to provide the scope with regard to the number of pathways, routes, or sources of pesticides required in the current OP cumulative assessment. CARES, a product of ACPA , is still under development. It is expected to be presented to the SAP in December, 2001.

LifeLine™ is a multi-pathway model that can be adapted to evaluate multiple chemicals. It focuses on identifying the periods during an individual's life where pesticide exposures are likely to occur, and identifying the source of those exposures. LifeLine™ produces a longitudinal estimate of possible exposures, focusing on looking across many years of a person's life. It draws upon a subset of natality records from the U.S. Census to develop the demographic characteristics of the population under evaluation. Consumption data from the CSFII are matched to the other information available using the demographic, regional and seasonal information from the two surveys. Residential exposure is estimated by linking data from a group of surveys to develop scenario characteristics that are anticipated to occur due to the use patterns of the group of chemicals under evaluation.

CARES is intended to perform cumulative and aggregate assessments, focusing on a population-based, cross-sectional analysis of a hypothetical year of exposure. CARES is anticipated to generate a series of exposure estimates moving across the calendar year, similar to that described for Calendex™. The demographic characteristics of the population being assessed will be drawn from a subset of the U.S. Census. CARES is intended to provide the user with a flexible, easily used tool to develop total and pathway-specific estimates of exposure, and to facilitate identification of the sources of exposure.

VI. Dietary Exposure Assessment

A. Dietary Exposure From Food

Dietary exposure from food is calculated considering what is eaten by individuals in one day and residue values for food. The food exposure assessment is extensively refined using probabilistic Monte Carlo analyses. Information on the amount of residues that may be on foods is obtained mainly from the USDA's Pesticide Data Program (PDP). PDP collects samples of selected food commodities throughout the year on a nationwide basis. These samples are analyzed for numerous pesticide residues and, therefore, capture co-occurrence of different pesticide residues on a particular sample. The distribution of residues that results from this program reflects a range of pesticide use patterns. It also takes into account the percentage of the crop nationwide to which each pesticide is typically applied (known as percent crop treated). PDP data are available for the commodities that have been directly monitored as part of the program and will also be used to estimate residues on commodities where this data can be reliably used as a surrogate (e.g., measured data for broccoli would be used to estimate cauliflower residues). In the case study presented to the SAP for the OPs, the refined food assessment is based upon PDP residue monitoring data only. Those commodities where neither PDP data are available, nor can PDP data from other commodities be used as a surrogate, were excluded from the analysis.

The Agency limited the food assessment to use of PDP monitoring data for several reasons. The PDP program is designed to provide the best available data for risk assessments. In the case study, the Agency made the assumption that use patterns of pesticides in food crops in the U.S. are implicit in the pattern of detectable residues found. That is, no additional adjustments of data for percent crop treated were made. In addition, only composite samples (e.g., 5 lbs of apples homogenized for one composite sample instead of analyzing a single serving of one apple) were used because the composite values are assumed to more closely reflect co-occurrence of multiple pesticides on the food items. Other available monitoring data are collected for different purposes than those of the PDP program and are not necessarily designed to reflect the overall consumption by the U.S. population. For example, the FDA surveillance data are based on commodities collected generally at different points in commerce than those collected by PDP. The FDA total diet study is excellent for assessing the occurrence of pesticides in foods that have actually been prepared for consumption; however, the number of samples analyzed is very small. The OP market basket study was submitted in late April, 2001 and is currently in review.

Consumption data used in the case study were taken from the USDA Continuing Survey of Food Intake by Individuals (CSFII 1994-96). This will be updated for the preliminary assessment to include data from the 1998 Supplemental Children's Survey. The CSFII records one-day food and nutrient intake data and is considered to be representative of the U.S. population. The database includes over 15,000 individuals and more than 35,000 unique person days of consumption information.

Of the 459 food commodities in the CSFII that were the basis of the assessment in the case study, 128 were included in the analysis either because they were directly included in PDP (74) or translation from PDP to other commodities was deemed acceptable (54). The other 331 commodities were not included in the analysis. Many of these commodities are not expected to contribute significantly to dietary exposure (e.g., spices and herbs). However, some notable exclusions include cranberries, cherries, peanuts, and rice. The case study accounts for approximately 90% of total dietary consumption by children, based on average children's consumption in the CSFII. Because 39% of children's total dietary consumption is water, approximately 17% of food consumption is not accounted for in the case study.

Comments from the SAP on the case study focused on two aspects of the analysis. In general, the SAP encouraged the Agency to avoid mixing different data sets–particularly data sets of different quality–in conducting its analyses; however, they also noted some concern about foods that were not covered in the assessment. Currently the Agency is examining, for foods not covered by the PDP program, the monitoring data available from other sources (FDA, market basket surveys, etc.); as well as other information on the likely impact on the risk estimates of excluding foods for which monitoring data are not available. EPA is examining, for example, how much of each excluded food item is consumed and by whom; and how and when the chemical is applied to that crop. In addition, EPA is analyzing the amount of the diet that is covered for relevant sub-populations when various sources of residue data are included or excluded from the analyses. The Agency is also examining whether it is appropriate to consider chemicals with consistent "no detects" in monitoring data to provide no quantitative contribution to the cumulative assessment.

Residues of organophosphates may be either concentrated or reduced by the activities of drying (e.g., prunes), processing (e.g., juice), washing, peeling and cooking. The Agency uses processing factors to account for these situations in the risk assessment. EPA has utilized, to the extent possible, the processing studies that have been submitted to the Agency in support of the registration and reregistration activities for individual pesticides. In cases where no acceptable data were available, the assessment relies on assumptions regarding processing factors. The case study lists in detail the available processing data.

B. Exposure From Water

Drinking water exposure to pesticides can occur through ground water and surface water contamination. Potential for exposure to pesticides in drinking water varies for different parts of the country and in different times of the year. Contributing factors to these differences include time of pesticide application and weather conditions shortly after application. These differences are also influenced by the inherent local andregional differences in soils, crops, and site vulnerabilities. To make the water assessments reflect geographic variations as realistically as possible, OPP plans to use USDA Economic Research Service maps to divide the continental United States into approximately 10 to 15 regions. These regions are grouped according to similarity in crops and take into account the geographic and climatic differences that lead to different agronomic practices, pest pressures, pesticide application methods and rates, and factors that affect pesticide transport to water. Water will be assessed within these regions. This regional approach will allow the assessments to account for effects on drinking water that are driven by the different characteristics of these regions.

Scenarios for developing estimates of pesticides in drinking water within the region will be chosen based on organophosphate use, watershed vulnerability (which accounts for such factors as pesticide runoff, potential for spray drift, etc.), and source of drinking water (surface water or ground water). Information on the use of different pesticides within the same region, the timing of use, and the fate and transport properties of the pesticides will be used to identify pesticides that are likely to co-occur. Factoring drinking water exposure into the framework for food exposures means developing a person-by-person approach to estimating drinking water exposure over time, which preserves the individual's demographic characteristics and associates only those exposures that are appropriate for such an individual, as described above in "Cumulative Exposure Models."

The planned probabilistic cumulative risk assessment for the organophosphates necessitates that drinking water exposures be based on daily concentrations of pesticides in the drinking water sources. When longer term exposure estimates are used, multiple sequential daily exposures would be averaged to obtain the relevant exposure estimate. To estimate risk, the assessment will use available monitoring data and modeled distributions of daily concentrations of pesticides in a probabilistic analysis. When EPA presented the cumulative OP case study to the SAP, water concentrations for two organophosphate compounds were estimated using a regression based model developed by USGS called Watershed Regression for Pesticides (WARP) which used monitoring data from 71 mid-Atlantic/Piedmont drinking water intakes. While the SAP comments on the WARP approach used in the case study were generally favorable, the panel suggested that further development of this modelwas necessary since it does not have a time component, i.e., it does not give daily concentrations which would allow Calendex™to link water and residential exposures in time. Thus, this model is not appropriate at this time for a probabilistic risk assessment based on daily exposure estimates.

1. Available Monitoring Data

EPA's three main sources of monitoring data for organophosphates in water are:

(1) USGS ambient water samples which include 11 of the OPs,

(2) ground and surface water monitoring information submitted by the registrants, and

(3) an American Crop Protection Association monitoring project looking at five OP pesticides. In some instances, additional monitoring data are also available through some state monitoring programs, such as in California.

The Agency is committed to using all available monitoring data as extensively as possible. Monitoring data were used extensively in the individual assessments and the Agency has relied on these assessments in developing its planned approach to the cumulative assessment. Monitoring data confirm that OPs do occur in drinking water sources and that co-occurrence is common. In addition to guiding the Agency in focusing its regional assessments, monitoring data will also be used for comparison to the modeling distributions for the cumulative assessment.

However,two main considerations make it difficult to base the cumulative assessment solely on monitoring data. First, the monitoring databases are not robust enough to assess even a single chemical over time in various regions of the country. Sampling is too infrequent to assess daily concentrations and there are no monitoring data for some compounds which makes it difficult to use the available data to assess the co-occurrence of multiple chemicals over time across the country. The available monitoring data will, however, be used where possible to help verify co-occurrence. Secondly, mitigation developed as the result of the risk management for individual OP chemicals often resulted in use deletions, lower application rates, and reduced numbers of applications. The available monitoring data do not reflect these changes.

In summary, although the quantitative assessment is likely to be based on modeled distributions used in a probabilistic assessment, water monitoring data will be used throughout the assessment in three main ways.

- Groundwater monitoring data will likely be used to assess the vulnerability of groundwater to organophosphates.

- Any available monitoring will be used as background information for scenario selection. The primary criterion for scenario selection will be use information, but available monitoring data will be considered.

- Monitoring data will be used to evaluate modeling results at every level of the assessment process.

2. Assessment Tools

The above considerations, together with recommendations from the SAP, resulted in the evaluation of modeling tools that would allow production of a time-linked regional assessment, which is as realistic as possible.

Ground Water

In those areas of the United States which receive their drinking water from ground water, the determination of the pesticide concentrations for use in cumulative risk assessment will be accomplished by using monitoring data from vulnerable ground water sources. The concentrations of these pesticides in ground water are not expected to be significant in most regions, nor are they expected to fluctuate dramatically over time due to the fate parameters (chemical properties) of the organophosphate class of compounds. This class is not very persistent or mobile in the environment which are characteristics necessary to move through soils and contaminate ground water.

Surface Water

After consideration of available predictive tools, EPA plans to use the PRZM/EXAMS (IR-PCA) model but has modified the model input by using scenarios and inputs that are specifically designed for performing drinking water assessments. The model simulates runoff into an index drinking water reservoir (IR) which is based on Shipman City Lake in Shipman, Illinois. In addition, changes have been made to other model input parameters to produce outputs that reflect more realistic predictions. For example, a regional as opposed to a national Percent Crop Area (PCA) is also being used in the model to account for the amount of land on which crops are grown in the different localities where the drinking water is being assessed. Also, instead of generating one conservative high end exposure number, the Agency plans to use all 13,000 plus daily concentration values to produce distributions that will be used in a probabilistic risk assessment for the different regions across the country. In addition, better crop-pesticide use information is being generated and, instead of using the maximum label rates, maximum numbers of applications, and minimal time intervals between applications, EPA will use typical rates, frequencies and intervals which again makes the model outputs more realistic and reflects the actual agronomic practices of the growers.

The Agency believes that this approach is the best methodology available to estimate daily residue concentrations in drinking water because it allows for the assessment of multiple chemicals, the data generated span a time frame of over 30 years which captures the variability due to changing weather conditions, distributions can be generated in different locations across the entire country thus capturing regional variability and, since daily distributions are generated, you can maintain the time dependency that is needed for this type of risk assessment. Because the entire distribution will be put into the Calendex™ model the differences in exposures on different days will be taken into account.

The differences in the individual chemical and cumulative approaches for the determination of pesticide concentrations in drinking water are summarized in the following table:

Aggregate Screening vs Cumulative Assessments

Aggregate Screening Assessment for A Single Pesticide	*Cumulative Assessment for Multiple Pesticides*
point estimate (single value), 99.9th percentile concentration	**distribution** of all daily concentrations (13,000+ days)
national estimate (single site represents entire US)	regional estimate (**multiple sites**, regional differences)
national Percent Crop Area (PCA)	regional PCA, reflecting variation in crop intensity
maximum label rates & frequency, minimum interval between applications	**typical rates**, frequencies, intervals
comparison of point estimate to DWLOC value	**probabilistic** assessment of water exposures
one compound at a time	**multiple compounds** considering co-occurrence

VII. Residential (& Other Non-occupational) Risk Assessment

Potential for exposure to pesticides from residential and other non-occupational uses differs in different parts of the country and at different times of the year. Contributing factors to these differences include amount and time of pesticide application. In order to make the residential assessments reflect spatial variation as realistically as possible, EPA plans to use USDA Economic Research Service maps to divide the continental United States into approximately 10 to 15 regions. These are the same regions used for the water assessments. This regional approach will allow the assessments to account for variation in residential exposures that are driven by spatial differences.

Exposures to pesticides can occur through dermal, inhalation, and non-dietary ingestion routes as a result of homeowner (i.e., “do-it-yourself”) and commercial applications in residential and public areas. Exposure can result from mixing, loading, and applying the pesticide, and/or reentering a treated site. Residential exposure to organophosphates in outdoor settings may result from applications to lawns, ornamentals, and "backyard" orchards and vegetable gardens. Indoor organophosphate exposures may result from crack and crevice treatments, applications to indoor potted plants, the use of foggers and resin pest strips, and from pet products (e.g., impregnated collars, dips, powders). Certain residential uses that can be assumed to result in negligible exposure (e.g., ant/roach bait stations in child resistant packaging or post-application exposure to treated fire ant mounds) will likely not be included in the assessment. That was the case in the individual chemical assessments, as well.

EPA also assesses post-application exposures in indoor/outdoor public areas such as parks, recreational areas, golf courses, schools or office buildings. Furthermore, the risk assessment includes residential bystander exposures from public health uses of organophosphates (e.g., mosquito and blackfly abatement).

The following chart delineates the current residential use picture for the organophosphates:

Residential Uses for the Organophosphates[1]

Chemical	*Indoor Residential Uses*	*Outdoor Residential Uses*	*Golf Course and Public Area Uses*	*Pet Uses*	*Public Health Uses*
acephate	Crack and crevice	Ornamentals, residential turf, sod farms	Golf course turf	N/A	N/A
bensulide	N/A	Residential turf	Golf course turf	N/A	N/A
chlorpyrifos	N/A	N/A	Golf course and sod farm turf	N/A	Mosquito adulticide
diclorvos (DDVP)	Resin pest strips, crack and crevice (professional applicators only)	Residential turf and ornamental plants (professional applicators only)	N/A	Flea collars, sponge, spray and dip (applied by veterinarians only)	N/A
disulfoton	Potted plant treatments	Flower gardens, roses, ornamentals, shrubs, small trees.	N/A	N/A	N/A
fenamiphos	N/A	N/A	Golf course turf	N/A	N/A
fenthion	N/A	N/A	N/A	N/A	Mosquito adulticide
malathion	N/A	Residential turf, ornamentals, garden, fruit trees.	Golf course turf, pick-your-own strawberries/orchards, turf in public areas	N/A	Mosquito adulticide
naled	N/A	N/A	N/A	Flea collars	Mosquito adulticide, black fly control
tetrachlorvinphos	N/A	N/A	N/A	Dips, powders, sprays, and flea collars.	N/A
trichlorfon	N/A	Residential turf and ornamentals	Golf course turf, turf in public areas	N/A	N/A

[1]For several of these chemicals, individual risk mitigation has not yet been completed. In these cases, all currently remaining uses will be considered in the cumulative assessment.

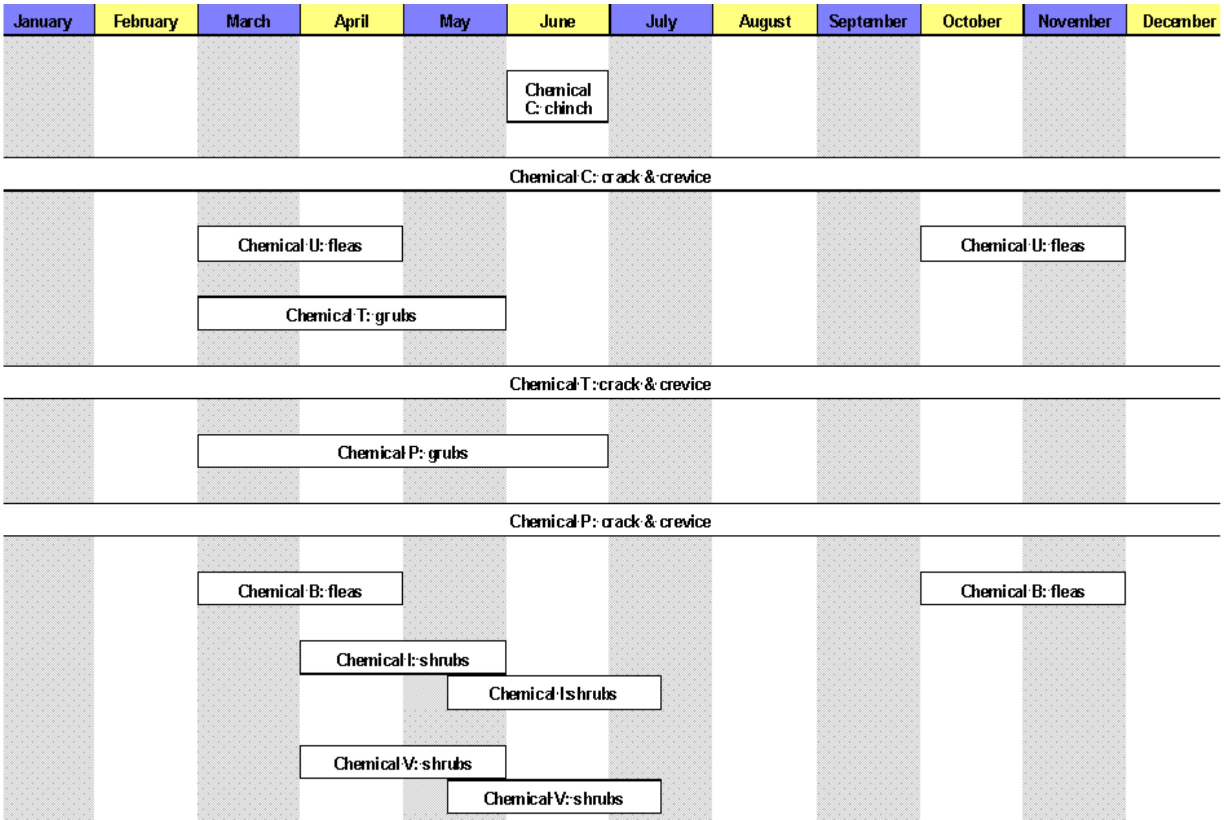
A. Spatial and Temporal Aspects of the Residential Assessment

Information relating to both the temporal and spatial aspects of exposure will be reflected in the residential portion of the cumulative risk assessment. The assessment will match exposure scenarios with uses representative of a particular region. The residential risk assessment scenarios will also be based on application timing, duration of use, and frequency of application for each chemical. For example, if you live in Buffalo, New York, and it's January, you will not be exposed to pesticides by mowing your lawn.

Chemical use patterns greatly affect potential exposure scenarios. By evaluating a pesticide's geographic and temporal pattern of use, a profile for each chemical can be developed to establish the potential routes, durations, and frequencies of exposure. Also, the evaluation of chemical use profiles allows for the identification of exposure scenarios that may overlap, co-occur, or vary among chemicals. These possible exposures will then be associated to individuals in the assessment, again preserving linkages to demographic characteristics of the individuals as well as appropriate linkages in uses. For example, in some cases the use of one product may affect the likelihood of using another product. This might be true with respect to products used for flea control: an indoor fogger, lawn care product, and a flea product for a pet might be more likely to be used simultaneously. In other cases, the products may serve essentially the same purpose, such that the use of one will almost certainly preclude the use of the other, that is, they are competitors. The chart on the following page (Figure 1) provides a visual example of the results of the likelihood and frequency assumptions for the assessment within one example region. It displays the various residential applications and their timing (including repeated applications) over the course of a year, for one region/site.

These likelihood and frequency assumptions for residential scenarios would be used to superimpose a pattern of relevant residential exposures that could reasonably be expected to occur throughout the year for a given individual/population member in the region. Any individual's exposure would then be based on probabilistic methods that preserve relevant product linkages and time, space, and demographic characteristics associated with the individual.

Figure 1. Example Region



EPA will use the Calendex™ model to perform an assessment which links spatial, temporal, and demographic aspects of the exposures. Currently, 50 residential "scenarios" (i.e., chemical/activity/route of exposure) can be accommodated in the Calendex™ model. Calendex™ will link all the exposures from food, drinking water, and non-dietary sources to individuals/population members in the CSFII database as discussed above in "Cumulative Exposure Models."

B. Hazard

The estimated exposures to each pesticide will be converted to index chemical equivalents using route-specific relative potency factors for oral, dermal, and inhalation exposures, as described above in "Endpoint Selection." Exposures will be compared to route-specific BMD_{10} 's of the index chemical to develop the resulting route-specific and total MOEs.

C. Use-Related Information

In general, the majority of use-related information in the cumulative risk assessment will be obtained from the National Garden Survey (1996-1997), the Certified/Commercial Pest Applicator Survey (1993), the National Pest Management Association Survey (2001), and the Occupational and Residential Exposure Task Force (ORETF). If necessary, information will be supplemented by the professional judgment of field professionals and OPP staff. The following listing provides additional information regarding use-related information.

❑ Pesticide Selection: EPA will use several sources to determine which specific pesticides are used in particular residential settings. These include the available survey information and recommendations from State Extension Services. Only one chemical will be assigned per scenario, even though other chemicals may overlap in use and timing. For example, if a homeowner treats the lawn for grubs, it is assumed he/she will use only one product instead of all possible products registered for use on lawns for grubs.

- ❏ Timing of Application: Professional applications are assumed to occur during weekdays, with all five days assigned equal probabilities. Homeowner applications are assumed to occur during the weekend with Saturday and Sunday applications assumed to occur with equal probability. The frequency of treatments and the seasonal use of pesticides is directly related to the appearance of pests. Information on pest appearance and pressure will be gathered from state recommendations (e.g., extension officers).

- ❏ "Do-it-yourself" Versus Professional Applications: A National Gardening Association study contains data on the number of households that participate in "do-it-yourself" lawn care. Information from the Professional Lawn Care Association of America regarding the percentage of applications made by consumers versus professional lawn care operators will also be considered.

D. Exposure Data

In general, data generated by the Outdoor Residential Exposure Task Force (ORETF) and data from the Pesticide Handler Exposure Database (PHED) form the basis of the exposure inputs for residential handlers. PHED data will be used sparingly because of uncertainties and limitations in some areas.

Post-application exposure estimates will mainly be derived from proprietary studies and published exposure studies. These studies were used to develop the transfer coefficients and turf transferable residue (TTR) estimates as well as to evaluate non-dietary ingestion and indoor air concentrations. If chemical-specific data are lacking, surrogate chemicals or formulations will be used in the assessment where appropriate. Other inputs to the residential exposure assessment are detailed below:

- ❏ Duration of Exposure: An EPA publication, *Exposure Factors Handbook*, will be used to determine distributions of time spent outdoors and indoors and the duration of exposure.

- ❑ Human Activity Patterns: Distributions of children's behavioral patterns are largely based on real-world observations reported by Reed, et al., 1998. While the Jazzercise™ data are used for assessing single route exposures in individual assessments, it will likely not be used in the OP cumulative assessment due to a concern for compounding conservatism. Instead, two studies (Black, 1993, “An Assessment of Children’s Exposure to Chlorpyrifos from Contact with a Treated Lawn” and Vaccaro, et al., 1996, “The Use of Unique Study Design to Estimate Exposure of Adults and Children to Surface and Airborne Chemicals”) may be used for developing transfer coefficients. Other aspects of children's exposure, such as the amount of residues available from each hand-to-mouth event, the frequency of mouthing events, the amount of saliva on children's hands, and the removal of residues on hands by saliva will be based on various proprietary and literature studies and advice from the SAP.

- ❑ Exposure Factors: Inhalation rates (which vary primarily by weight, gender, age and activity level) are derived from EPA's *Exposure Factors Handbook*, together with demographic information linked to the particular individuals/population members in the CSFII database.

- ❑ Residential Building Factors: Indoor air concentration data are available in proprietary studies or published literature.

- ❑ Product Characteristics: The physical and chemical properties of the pesticide (e.g., molecular weight, vapor pressure, break down to other chemicals, etc.) also will be used to determine the chemical rate of evaporation into the air, how much of the pesticide will transfer (e.g., from lawn to hands, from hands to mouth, etc.), and its rate of degradation.

E. Individual Versus Cumulative Assessment

In general, the individual chemical assessments are designed to reflect reasonable high-end risks to the individuals/population members represented in each exposure scenario (e.g., adults applying to lawn with push-type spreader, children playing on treated lawns). Because the cumulative risk analysis will combine many data sets into a single assessment, it is important to reduce the likelihood of compounding conservative assumptions and over-estimation bias. Therefore, it is important to provide estimates of potential exposure that appropriately bound the risks while realistically capturing possible multiple exposures.

The cumulative residential risk assessment will evaluate residential exposures in a probabilistic manner, similar to the dietary analyses. This probabilistic risk assessment takes into account all available information and considers variability and the probability of occurrence for the entire population. The cumulative residential assessment modeling will be run using a range of rates with a range of numbers of applications (instead of labeled maximum rates and maximum numbers of applications used in the individual assessments), which will result in a distribution of residue levels. For example, some individuals may get their homes treated for roaches every month while others never treat their homes. Thus, residues of insecticide "X" may vary from no residue (based on non-treatment or use of an alternative chemical) up to some maximum concentration of insecticide X, based on exposure and usage information. In the sampling, a zero would be selected a certain percentage of the time to account for non-treatment or alternative treatment, and various residue values for insecticide X would be selected the rest of the time. The values are selected randomly, while preserving the demographic characteristics of the individuals in the CSFII and other appropriate linkages in exposure. The values are then used by Calendex™ to generate a distribution of exposures for the populations of concern. The risk estimate will be expressed as a distribution of values rather than as a point estimate, which is the case in the individual risk assessments.

VIII. Occupational and Ecological Risk Assessment

Cumulative occupational and ecological risk assessments are not required by FQPA and have not been conducted. Occupational and ecological risks were addressed in the individual risk assessments for the OPs.

IX. Summary of Pending Data

- The OP market basket survey was received in late April, 2001 and is currently in review. This review is expected to be completed by August, 2001 to allow inclusion of this information in the preliminary OP cumulative risk assessment, as appropriate.

- The analysis of the national Pest Management Association 2001 "Pest Control Operators Use and Usage Information Survey" is underway. This information will be incorporated in the assessment as appropriate.

- The Apple Processors Association 2001 "Determination of Organophosphate and Carbamate Pesticides and Their Major Metabolites in Commercially Processed Applesauce" is also in review. The EPA expects to complete this review by August, 2001 to allow inclusion in the preliminary risk assessment, as appropriate.

List of Abbreviations

a.i.	Active Ingredient
AGDCI	Agricultural Data Call-In
AR	Anticipated Residue
ARC	Anticipated Residue Contribution
BCF	Bioconcentration Factor
BMD	Benchmark Dose
BMR	Benchmark Response
CAG	Cumulative Assessment Group (of chemicals)
CMG	Common Mechanism Group (of chemicals)
CNS	Central Nervous System
CWS	Community Water Systems
CSF	Confidential Statement of Formula
CFR	Code of Federal Regulations
CSFII	Continuing Surveys for Food Intake by Individuals (from USDA)
DCI	Data Call-In
DEEM	Dietary Exposure Evaluation Model
DFR	Dislodgeable Foliar Residue
DWLOC	Drinking Water Level of Comparison.
EC	Emulsifiable Concentrate Formulation
ED_{10}	Effective Dose: central estimate on a dose associated with a 10% response adjusted for background.
EEC	Estimated Environmental Concentration–The estimated pesticide concentration in an environment, such as a terrestrial ecosystem.
EP	End-Use Product
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FFDCA	Federal Food, Drug, and Cosmetic Act
FQPA Food Quality Protection Act	
G	Granular Formulation
GIS	Geographical Information System
GLC	Gas Liquid Chromatography
GLN	Guideline Number
GM	Geometric Mean
GRAS	Generally Recognized as Safe as Designated by FDA
HDT	Highest Dose Tested
ILSI	International Life Sciences Institute
IR	Index Reservoir

LC_{50}Median	Lethal Concentration–A statistically derived concentration of a substance that can be expected to cause death in 50% of test animals. It is usually expressed as the weight of substance per weight or volume of water, air or feed, e.g., mg/L, mg/kg or ppm.
LCO	Lawn Care Operator
LD_{50}Median	Lethal Dose–A statistically derived single dose that can be expected to cause death in 50% of the test animals when administered by the route indicated (oral, dermal, inhalation). It is expressed as a weight of substance per unit weight of animal, e.g., mg/kg.
LED_{10}	Lower Limit on an Effective Dose (95% lower confidence limit on a dose associated with 10% response adjusted for background)
LEL	Lowest Effect Level
LOC	Level of Concern
LOD	Limit of Detection
LOAEL	Lowest Observed Adverse Effect Level
MCLG	Maximum Contaminant Level Goal (MCLG)–The MCLG is used by the Agency to regulate contaminants in drinking water under the Safe Drinking Water Act.
mg/kg/day	Milligram Per Kilogram Per Day
mg/L	Milligrams Per Liter
MOE	Margin of Exposure
MP	Manufacturing-Use Product
MPI	Maximum Permissible Intake
MRID	Master Record Identification (number)–EPA's system of recording and tracking studies submitted.
N/A	Not Applicable
NAS	National Academy of Sciences
NAWQA	USGS National Water Quality Assessment
NOEC	No Observable Effect Concentration
NOAEL	No Observed Adverse Effect Level
NPDES	National Pollutant Discharge Elimination System
NR	Not Required
NRC	National Research Council
OP	Organophosphate
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides and Toxic Substances
ORETF	Occupational and Residential Exposure Task Force
PAD	Population Adjusted Dose
PADI	Provisional Acceptable Daily Intake
PAG	Pesticide Assessment Guideline
PAM	Pesticide Analytical Method
PCA	Percent Crop Area
PCO	Pest Control Operator

PDP	Pesticide Data Program (USDA)
PHED	Pesticide Handler's Exposure Database
PoC	Point of Comparison
PoD	Point of Departure
ppb	Parts Per Billion
ppm	Parts Per Million
PRN	Pesticide Registration Notice
PRZM/ EXAMS	Pesticide Root Zone Model/EXposure Analysis Model System–Coupled models used to estimate pesticide concentrations in surface water.
RAC	Raw Agriculture Commodity
RBC	Red Blood Cell
RED	Reregistration Eligibility Decision
REI	Restricted Entry Interval
RfD	Reference Dose
RPF	Relative Potency Factor
RUP	Restricted Use Pesticide
SAP	FIFRA Scientific Advisory Panel
SCI-GROW	Tier I Ground Water Computer Model
SF	Safety Factor
SLN	Special Local Need (Registrations Under Section 24© of FIFRA)
SOP	Standard Operating Procedures
TC	Toxic Concentration–The concentration at which a substance produces a toxic effect.
TD	Toxic Dose–The dose at which a substance produces a toxic effect.
TEP	Typical End-Use Product
TGAI	Technical Grade Active Ingredient
TLC	Thin Layer Chromatography
TMRC	Theoretical Maximum Residue Contribution
torr	A unit of pressure needed to support a column of mercury 1 mm high under standard conditions.
TRR	Total Radioactive Residue
UF	Uncertainty Factor
μg/g	Micrograms Per Gram
μg/L	Micrograms Per Liter
USDA	United States Department of Agriculture
USGS	United States Geological Survey
UV	Ultraviolet
WARP	Water Analysis Regression Program
WHO	World Health Organization
WP	Wettable Powder

Glossary of Terms

Absorbed Dose: The amount of a substance penetrating across the absorption barriers (the exchange barriers) of an organism, via either physical or biological processes. Synonymous with internal dose.

Additivity: When the "effect" of a combination of chemicals is estimated by the sum of the exposure levels or the effects of the individual chemicals.

Aggregate Dose: The amount of a single substance available for interaction with metabolic processes or biologically significant receptors from multiple routes of exposure.

Aggregate Exposure: The amount of a chemical available at the biological exchange boundaries (e.g., respiratory tract, gastrointestinal tract, skin) for all routes of exposure.

Aggregate Exposure Assessment: A process for developing an estimate of the extent of a defined population to a given chemical by all relevant routes and from all relevant sources.

Aggregate Risk: The risk associated with all pathways & routes of exposure to a single chemical.

Analog(s): Analog is a generic term used to describe substances that are chemically closely related. Structural analogs are substances that have similar or nearly identical molecular structures. Structural analogs may or may not have similar or identical biological processes.

Antagonism: The ability of a substance to prevent or interfere with another substance interacting with its biological targets, thereby reducing or preventing its toxicity.

Benchmark Dose (BMD_L): A statistical lower confidence limit on the dose producing a predetermined level of change in adverse response compared with background response. The BMD is derived by fitting a mathematical model to the dose-response data. A BMD_{10} is a benchmark dose with 10% change in adverse response compared with background response.

Biomonitoring: Measurement of a pesticide or its metabolites in body fluids of exposed persons, and conversion to an equivalent absorbed dose of the pesticide based on a knowledge of its human metabolism and pharmacokinetics.

Common Mechanism of Toxicity: Common mechanism of toxicity pertains to two or more pesticide chemicals or other substances that cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (i.e., interpreted as mode of action). Hence, the underlying basis of the toxicity is the same, or essentially the same, for each chemical.

Common Mechanism Group (CMG): A group of pesticides determined to cause adverse effects by a common mechanism of toxicity. The CMG is defined using the previously released "Guidance for Identifying Pesticide Chemicals and Other Substances that Have a Common Mechanism of Toxicity" (February 5, 1999). Not all members of a CMG will necessarily be incorporated in the cumulative risk assessment.

Common Toxic Effect: A pesticide and another substance that are known to cause the same toxic effect in or at the same anatomical or physiological site or locus (e.g., the same organ or tissue) are said to cause a common toxic effect. Thus, a toxic effect observed in studies involving animals or humans exposed to a pesticide chemical is considered common with a toxic effect caused by another chemical if there is concordance with both site and nature of the effect.

Concurrent Exposure: The potential human exposure by all relevant pathways & routes that allows one chemical to add to the exposure of another chemical such that the total risk of a group of common mechanism chemicals is an estimate of the sum of the exposures to the individual chemicals. The accumulation of the common toxic effect may or may not depend on simultaneous or overlapping exposures depending on the duration and recovery time of the toxic

Cumulative Assessment Group (CAG): A subset of the CMG. The CAG is that group of pesticides selected for inclusion in the cumulative risk assessment. The chemicals in the CAG are judged to have a hazard and exposure potential that could result in the expression of a cumulative risk.

Cumulative Dose: The amount of multiple (two or more) substances which share a common mechanism of toxicity available for interaction with biological targets from multiple routes of exposure.

Cumulative Exposure Assessment: A process for developing an estimate of the extent to which a defined population is exposed to two or more chemicals which share a common mechanism of toxicity by all relevant routes and from all relevant sources.

Cumulative Toxicity or Toxic Effect: A cumulative toxic effect(s) is the net change in magnitude of a common toxic effect(s) resulting from exposure to two or more substances that cause the common toxic effect(s) from a common mechanism, relative to the magnitude of the common toxic effect(s) caused by exposure to any of the substances individually.

Cumulative Risk: For the purpose of implementation of FFDCA as amended by FQPA, cumulative risk is the likelihood for the cumulation of a common toxic effect resulting from all pathways and routes of exposure to substances sharing a common mechanism of toxicity.

Dependent (events): The probability of one event occurring is affected by whether or not another event has or has not occurred.

Deterministic: This approach uses point estimates, for example, single maximum values or average values, to represent input variables in an exposure model. This can be compared to a probabilistic approach which considers the full range of potential exposures incurred by members of a population.

Dislodgeable Residues: The portion of a pesticide (which may or may not include its metabolites) that is available for transfer from a pesticide treated surface.

Dose: The amount of substance available for interaction with metabolic processes or biologically-significant receptors after crossing the outer boundary of an organism.

Dose Rate: Dose per unit time (e.g., mg/day). Also called dosage. Dose rates are often expressed on a per unit-body-weight basis (mg/kg/day). Dose rates may also be expressed as an average over a time period (i.e., lifetime).

Dose Additivity: When the effect of a combination of chemicals is the effect expected from the equivalent dose of an index chemical. The equivalent dose is the sum of component doses scaled by their potency relative to the index chemical

Effective Dose (ED): The effective dose is a measured or estimated dose level associated with some designated level or percent of response relative to the control or baseline level of response. For example, the ED_{10} is a dose associated with a 10% response. The effective does is essentially the same as a benchmark dose (BMD). It is determined by using a curve-fitting procedure that is applied to the dose-response data for a chemical.

Exposure: Contact of a substance with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact.

Exposure Assessment: The qualitative or quantitative determination or estimation of the magnitude, frequency, duration, and rate of exposure of an individual or population to a chemical.

Exposure Scenario: A combination of facts, assumptions, and inferences that define a discrete situation or activity where potential exposures may occur.

Independent (events): The probability of one event occurring is not affected by whether or not another event has or has not occurred.

Index Chemical: The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical should have a clearly defined dose-response relationship.

LED_{10}: The lower confidence limit on an effective dose, that is, in this case the 95% lower confidence limit on a dose associated with 10% response adjusted for background.

Level of Comparison: A drinking water level of comparison is a theoretical upper limit on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food, drinking water, and through residential uses.

Lowest Observed Adverse Effect Level (LOAEL): The lowest does at which an adverse effect is seen.

Margin of Exposure: The point of departure divided by a human environmental exposure(s) of interest, actual or hypothetical.

Mechanism of Toxicity: Mechanism of toxicity is defined as the major steps leading to an adverse health effect following interaction of a substance with biological sites. All steps leading to an effect do not need to be specifically understood. Rather, it is the identification of the crucial events following chemical interaction that are required in being able to describe a mechanism of toxicity.

Monte Carlo Analysis: One of several mathematical techniques for performing probabilistic assessments. The method relies on the computational powers of modern computers to simulate the range and frequency of all possible outcomes of a process based on repeatedly sampling from the inputs provided by the user. These inputs are combined according to the model that is specified by the user.

No Observed Adverse Effect Level (NOAEL): The dose at which no adverse toxic effect is seen.

Pathway of Exposure: The physical course a pesticide takes from the source to the organism exposed (e.g., through food or drinking water consumption or residential pesticide uses).

Point of Comparison (PoC): Dose at which a uniform response occurs.

Point of Departure (PoD): Point on the dose-response curve where each chemical's response is close to or within the background level of response, in other words, the dose at which effects from a pesticide are first distinguishable. Depending on the kind of data available and the purpose of the analysis, there are differing procedures for estimating the point of departure.

Population Adjusted Dose (PAD): The RfD adjusted for the FQPA safety factor.

Reference Dose (RfD): NOAEL/UF.

Relative Potency Factor (RPF) Method: The RPF approach expresses the potency of each chemical in a CAG in relation to the potency of another member in the group which has been selected as the index chemical. A relative potency factor is calculated for each chemical for each route of exposure (e.g., oral, dermal, inhalation). For example, if compound A is determined to be one-tenth as toxic as the index compound the RPF for compound A is 0.1. Using this approach, for each route of exposure for each chemical, exposure is expressed as exposure equivalents of the index chemical. The exposure equivalents are calculated by multiplying the residues and the RPF for each route. These exposure equivalents are summed to obtain an estimate of total exposure by route in terms of the index chemical.

Route of Exposure: The way a chemical enters an organism after contact, e.g., ingestion, inhalation, or dermal absorption. Note that all three routes of exposure can occur within an exposure pathway. A pathway is not route specific.

Site of Toxic Action: The physiological site(s) where a substance interacts with its biological target(s) leading to a toxic effect(s).

Structure-Activity Relationships: Substances that contain or are bioactivated to the same toxophore may cause a common toxic effect by a common mechanism. The relative toxic efficacy and potency among the substances in their ability to cause the toxic effect may vary substantially. Differences in potency or efficacy are directly related to the specific or incremental structural differences between the substances and the influence these differences have on the ability of the toxophore to reach and interact with its biomolecular site of action, and on the intrinsic abilities of the substances to cause the effect. The ability of two or more structurally-related substances to cause a common toxic effect and the influence that their structural differences have on toxic efficacy and potency are referred to as structure-activity relationships.

Surrogate Data: Substitute data or measurements on one substance (or population) used to estimate analogous or corresponding values for another substance (or population).

Toxic Action: The interaction with biological targets that leads to a toxic effect.

Toxic Effect: An effect known (or reasonably expected) to occur in humans that results from exposure to a chemical substance and that will or can reasonably be expected to endanger or adversely affect quality of life.

Toxic Endpoint: A quantitative expression of a toxic effect occurring at a given level of exposure. For example, acute lethality is a toxic effect, an LD_{50} value (median lethal dose) is the toxic endpoint that pertains to the effect.

Toxic Potency: The magnitude of the toxic effect that results from a given exposure. Relative potency refers to comparisons of individual potencies of chemicals in causing a common toxic effect at the same magnitude (e.g., LD_{50}, ED_{50}) by a common mechanism.

Transfer Coefficient: Residue transfer rate to humans during the completion of specific activities (e.g., cm^2 per hour), calculated using concurrently collected environmental residue data.

Uncertainty: Lack of knowledge about specific factors, parameters, or models.

Uncertainty Factor: Uncertainty factors applied to account inter- and intra-species differences in relation to toxic effects, and uncertainties associated with the data.

Unit Exposure: The amount of a pesticide residue’s to which individuals are exposed, normalized by the amount of active ingredient used.

Variability: Differences attributed to true heterogeneity or diversity in a population or exposure parameter.

Weight-of-the-Evidence: Weight-of-the-evidence refers to a qualitative scientific evaluation of a chemical substance for a specific purpose. A weight of evidence evaluation involves a detailed analyses of several or more data elements, such as data from different toxicity tests, pharmacokinetic data, and chemistry data followed by a conclusion in which a hypotheses is developed, or selected from previous hypotheses.